Ref. 4

U. S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
June 1999

Food Advisory Committee Meeting, June 24-25, 1999

06/25/99 Draft Report of the
FOOD ADVISORY COMMITTEE
DIETARY SUPPLEMENT WORKING GROUP
On

INGREDIENT IDENTITY TESTING RECORDS AND RETENTION

PREFACE

Current Good Manufacturing Practices (GMP) guidance is needed to assist a firm in selecting the appropriate tests to identify dietary supplement ingredients. Section 402(g)(2) of the Federal Food, Drug, and Cosmetic Act (the act) states that GMP regulations may not impose standards for which there are no current and generally available analytical methodologies. Analytical methodologies are available for identification of some dietary supplements such as vitamins and minerals, but a comprehensive compendium of generally available scientifically validated tests for identification of dietary ingredients has not been compiled. In particular, valid analytical methodologies are not available for many dietary ingredients, for example, botanicals and biologicals such as blood products, organ tissue, cartilage, and etc.

Morphological characters and organoleptic characteristics are used in some cases to validate the identity of botanical ingredients at the time of collection or for unprocessed botanicals. When sufficient morphological characters are present to separate the plant species from other plant species, then an accurate identification can be made since morphological characters are the sole basis of distinguishing most of the world's plant species. However, unprocessed botanicals that do not contain all the plant parts necessary to include adequate morphological characters to assure the correct species should have other identity aids or tests to assure the identity of the botanical. Greater detail on botanical ingredient identification is presented in the outline that follows.

Confirming dietary supplement ingredient identity and safety of animal origin products employ specific technical analytical and record keeping approaches. It

is possible that confirming identity and safety of biological ingredients may involve a combination of analyses designed to determine the presence of animal and plant matter and to differentiate family/species and tissue. Records and reports are needed to assure that products that are manufactured with bovine-derived materials at foreign sites or by foreign manufactures are free of disease and follow appropriate USDA regulations and that products that are manufactured with fish and fishery product materials follow appropriate FDA HACCP regulations. More detailed information on these issues follows in the Report outline.

The misidentification of dietary ingredients used in dietary supplements can present significant public health and economic concerns. GMP guidance is needed to assist a firm in following quality control and other written procedures, such as record keeping, necessary to ensure that dietary supplements are produced under conditions that will result in a safe and properly labeled product. Written procedures for manufacturing processes (e.g., master production and control records and batch production and control records) are necessary to ensure that good manufacturing procedures can be followed on a day-to-day basis. The written procedures are the standard-based criteria for evaluating day-to-day manufacturing operations. Data records from the day-to-day operations and evaluations are used to ensure that the dietary supplement products have the identity, purity, and strength they are represented to posses. Additionally, written procedures for handling complaints and records of reported complaints involving illnesses and injuries regarding dietary supplements are useful in periodic trend analyses to determine whether a reported injury or illness constitutes a serious public health problem.

The Center for Food Safety and Applied Nutrition (CFSAN), FDA asked its Food Advisory Committee (FAC) to form a GMP Working Group to consider two topics: 1) dietary supplements ingredient identity testing and 2) records and retention.

The GMP Working Group addressed the following FDA charges to the FAC:

Dietary Supplements GMP/Adequate Testing for Identity of Ingredients: The Working Group was asked to consider what constitutes "adequate testing" for identity of different dietary ingredients used in dietary supplements. What is needed to identify or provide assurance of the identity of a dietary ingredient, both when analytical tests are generally available and when analytical methods are not generally available? The Working Group outline

> Identifies the principles and questions a manufacturer would need to consider when selecting or designing a process to ensure the identity of a dietary ingredient. The criteria addresses
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> > a) The nature of the ingredient (e.g., a vitamin, mineral, amino acid, herb or botanical, or other dietary supplement ingredient);

b) The form of the ingredient (e.g., whole botanical, powder, or extract); and

c) Special contents of the ingredient if relevant to the ingredient's identity (i.e., level of a chemical(s), such as a marker compound, in the botanical ingredient to distinguish the special contents of the botanical ingredient from other botanical ingredients from the same species of plant).

Includes citations to reference sources or compendia of available identity tests for botanical characters, molecular biological assays, chemical content and physical forms.

Identifies factors to be considered in development of a new method for providing the assurance of the identity of a dietary ingredient.

Includes criteria a dietary supplement manufacturer should use to determine if a particular identity test is the most appropriate method of providing assurance of the identity of a dietary ingredient.

Includes scientific or technical criteria a dietary supplement manufacturer should consider when determining if

a) Botanical characteristics, including morphological, anatomical, and/or organoleptic characteristics of the ingredient are sufficient and therefore the most appropriate means of providing assurance of the identity of a dietary ingredient;

b) A Certificate of Analysis (CofA) is the most appropriate method of providing assurance of the identity of a dietary ingredient; and

c) A microscopic and/or chemical test is the most appropriate method of providing assurance of the identity of a dietary ingredient.

Dietary Supplements GMP/Records and Retention: The Working Group was asked to consider what records are necessary to demonstrate that product safety is maintained throughout the manufacturing and distribution process, i.e., that dietary supplements have been produced under good manufacturing practices. The Working Group outline

Identifies records that are necessary to ensure that the identity, purity, composition, and quality of the dietary supplement will not adversely affect public health.

Identifies additional records that could assure dietary supplement manufacturers that GMPs are maintained throughout all their

manufacturing, including safety controls in computer controlled/assisted operations and records of internal quality audits.

Identifies records that are needed to evaluate reports of injuries or illnesses associated with a product including production and distribution records (e.g., lot or batch numbers, distribution information, reserve samples) and records needed to facilitate product recall.

I. INTRODUCTION

Dietary supplements are regulated under the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Dietary Supplement Health and Education Act of 1994 (DSHEA, P.L. 103-417). A dietary supplement means any ingested product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following ingredients: a vitamin; a mineral; an herb or other botanical; an amino acid; a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any ingredient described (see 201(ff) of the Act.)

Dietary supplements may not contain dietary ingredients that present a significant or unreasonable risk of illness or injury (see section 402(f) of the Act) or that may render the supplement injurious to health (see section 402 (a)(1) of the Act). The manufacturer bears the responsibility for ensuring that its dietary supplement products are safe. The DSHEA amendments grant authority to the Secretary, as delegated to the FDA, to establish GMP regulations governing the preparation, packing, and holding of dietary supplements under conditions that ensure their safety (see section 402(f) (1) of the Act).

Purpose of the Working Group Report

The FAC/GMP Working Group includes membership from the FDA FAC as well as special liaisons from the dietary supplement industry. The Report includes the recommendations to the FDA via the FAC concerning GMPs for dietary supplements specific to ingredient identity testing and records/records retention.

This Report provides guidance in selecting the most appropriate and reliable test(s) for dietary supplement ingredients. In responding to the FAC charge relating to dietary supplement ingredient identity testing, this Report takes a narrow definition of ingredient identity testing, i.e., testing to establish the origin, nature, characteristics, form and taxonomic classification (where applicable) of dietary supplement ingredients as defined by statute. A broader definition of ingredient identity testing that would address microbial and chemical contamination is beyond the scope of the Working Group ingredient identity testing charge. Adulteration is an important issue and

needs to be included in the full GMP regulation and related guidance to ensure the purity, composition, and quality of the dietary supplement. Principles used in selecting ingredient identity tests are also appropriate in selecting tests to detect adulteration; notation in this regard is included in the Report. The Working Group understands that FDA will address the issue of contaminants and adulteration within the full scope of GMP regulations.

This Report is not prescriptive; it does not recommend specific test procedures or acceptance criteria but provides general principles for consideration in the setting of performance standards for tests. Performance standards must be sufficiently accurate to distinguish or separate the ingredient from other ingredients that could adulterate or be confused with it. The goal of identity testing is to assure the public that what is on the product label is true and accurate. There are several steps in achieving this goal. One is confirming the ingredient identity provided by a supplier's certificate of analysis (CofA). It is possible that the CofA may or may not be complete. If the certificate is not complete, it is the obligation of the manufacturer to fill in the gaps and confirm the ingredient identity as well as to institute a quality assurance process to verify the reliability of the supplier's CofA. A firm can require suppliers to do tests in advance as part of supplier specifications, perform tests on site, or send a sample to a third-party laboratory for testing. All of these are elements of making sure the label is accurate. The testing performance standards should be based on a combination of vendor audits, ingredient specifications, and a sufficient number of identity tests conducted with the necessary frequency to insure that the product is actually what is stated on the label on a batch-to-batch basis. For final or finished products, the manufacturer needs to have a system that assures the identity of all the ingredients in the final product.

The Report also provides guidance in developing and maintaining records necessary to ensure that dietary supplements are produced under conditions that will result in a product that is not adulterated and is properly labeled. In responding to the FAC charge related to record keeping, all ingredient tests are addressed including ingredient identity, contamination, and adulteration. The record keeping section has been written to generally follow the format of the FDA Advanced Notice of Proposed Rulemaking for Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements, of February 6, 1997. The general goal of record keeping from a public health perspective is to assure product safety by developing written procedures for manufacturing, documenting that the written procedures are followed on a day-to-day basis, and maintaining records for tracing the manufacturing process forward and backward when adverse events are associated with a product.

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II. Organization of the Outline:

The outline portion of the Report first presents a glossary of terminology. Following this, the two charges to the Working Group regarding GMPs are addressed, i.e., adequate testing for identity of ingredients and records and records retention.

The general principles to be considered in determining the appropriate ingredient tests are outlined. Included are characteristics of the dietary supplement ingredient, of the test techniques available, of the testing environment, and of the ingredient test method validation. Characteristics of the ingredient type follow the dietary supplement categories specified in DSHEA without further definition.

Testing techniques include macroscopic/organoleptic, microscopic, and chemical. The conditions affecting the conduct of the tests, i.e., the testing environment, are personnel, equipment, and laboratory supplies.

For records and retention, the outline generally follows the manufacturing process with sections for records pertaining to personnel, receiving ingredients, testing ingredients, production, distribution, and post distribution complaints. The need for written operational procedures and records to document their day-to-day use, as well as quality control materials and documents are addressed.

Topical detail is provided in several appendices. Appendices include reference citations for various aspects of testing, e.g., for available test methodologies, determining test method validity, and selecting a representative sample from a batch/lot. The appendices also include desirable elements in a CofA a checklist useful in evaluating a supplier's CofA, a survey for evaluating the ability of a supplier's operation to produce wholesome and pure products, and a case study.

III. Glossary.

Acceptance Criteria: Acceptance criteria means the product specifications such as specified limits for the amount of the ingredient, amount or presence of contaminants, impurities, and foreign material, and etc., that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).

Adulteration: A food shall be considered to be adulterated if it bears or contains any poisonous or deleterious substance which makes it injurious to health as defined by the Food, Drug, and Cosmetic Act, section 402, and as

appropriate in accordance with 21 CFR §110 Food, § 113 Thermally Processed Low-Acid Foods Packaged in Hermetically Sealed Containers, § 123 Fish and Fishery Products, and § 131 Milk and Cream.

AOAC: AOAC International, formerly the Association of Official Analytical Chemists, methods are recognized worldwide as authoritative because of their thorough and rigorous testing and characterization. Where the method of analysis is not prescribed in a regulation, it is the policy of the US Food and Drug Administration in its enforcement programs to utilize the methods of analysis of the AOAC as published in the latest edition (13 Ed., 1980) of their publication "Official Methods of Analysis of the Association of Official Analytical Chemists," and the supplements thereto.

Batch: Batch or lot means a specific quantity of a dietary ingredient, dietary supplement, or other material that is intended to have uniform composition, character, and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

Botanical: Botanical means plant or plant parts including bark, woods, leaves, stems, roots, flowers, fruits, seeds, berries, or parts thereof, as well as exudates. Botanical raw material means fresh or processed (i.e., cleaned, frozen, dried, sliced, etc.) plant materials, macroscopic fungi, or algae for the manufacture of dietary supplements. Different parts of the same plant, fungus, or alga are considered distinct botanical raw materials if they can be used separately for their respective values.

A botanical product means a finished, labeled product that contains as ingredients vegetal matters or their constituents, which include, but are not limited to: plant materials, algae, macroscopic fungi, etc., or combinations thereof.

Certificate of Analysis: A certificate of analysis is a statement from the supplier about the identity, strength, quality, and purity of a dietary supplement raw material or ingredient or finished product.

Cultivated: Cultivated means botanical plants that are produced (grown or tended) as a crop.

Dietary Ingredient: Dietary ingredient means any raw or processed ingredient intended for use in the manufacture of a dietary supplement, including those that may not appear in such finished product including dietary ingredients as defined in 21 USC 321 (ff) and 21 USC 321(5).

In-Process Material: In-process material means any material fabricated, compounded, blended, ground, extracted, sifted, sterilized, derived by chemical reaction or processed in any other way that is produced for, and

used in, the preparation of a dietary product.

Manufacture: Manufacture or manufacturing includes all operations associated with the production of dietary products, including the firm or person who receives botanical raw materials in whole form, whether fresh (i.e., not dehydrated) or dried, for any processing other than dehydration (including but not limited to cleaning, grinding, tableting, encapsulating, extracting, etc.), whether for further distribution or for direct use in manufacturing; packaging and labeling operations; testing; and quality control of a dietary ingredient or dietary supplement.

Microorganism: Microorganisms or microbial when used as an adjective means yeasts, molds, bacteria, and viruses and includes, but is not limited to, species having public health significance.

Processor: Processor means a manufacturer (a firm or person) who receives botanical raw materials in whole form, whether fresh (i.e., not dehydrated) or dried, for any processing other than dehydration (including but not limited to cleaning, grinding, tableting, encapsulating, extracting, etc.), whether for further distribution or for direct use in manufacturing.

Representative Sample: Representative sample means a sample that consists of a number of units that are drawn based on rational criteria, such as random sampling, and is intended to assure that the sample accurately portrays the material being sampled.

Specification: A specification is a list of tests, references to analytical procedures, and appropriate acceptance criteria with numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a substance or dietary supplement product, or materials at other stages of their manufacture should conform to be considered acceptable for their intended use. Specifications are one part of a total control strategy designed to ensure product quality and consistency. Specifications for assuring the identity of an ingredient should be sufficiently precise to distinguish the ingredient from other ingredients that could be confused with the desired ingredient including potential and known adulterants.

Standard Reference Material: A reference material is a highly purified compound that is well characterized. Two categories of reference materials are 1) compendial reference standard (e.g., USP/NF) that does not need characterization and 2) non-compendial standard that should be of the highest purity that can be obtained by reasonable effort and should be thoroughly characterized to assure its identify, strength, quality and purity.

If a compendial reference standard is not available, the manufacturer should have established appropriately characterized in-house primary

reference materials, prepared from lot(s) representative of production and clinical materials. In-house working reference material(s) used in the testing of production lots should be calibrated against this primary reference material. Where an international or national standard is available and appropriate, reference materials should be calibrated against it. While it is desirable to use the same reference materials for both biological assays and physiochemical testing, in some cases, it is possible that a separate reference material may be necessary. Also, it is possible that distinct reference materials for product-related substances, product-related impurities, and process-related impurities may need to be established.

In-house primary reference materials: A primary reference material is an appropriately characterized material prepared by the manufacturer from a representative lot(s) for the purpose of biological assay and physiochemical testing of subsequent lots and against which in-house working reference material is calibrated. The in-house reference material should be sufficiently well characterized to assure the accurate identity of the reference material.

In-house working reference material is a material prepared similarly to the primary reference material and is established solely to assess and control subsequent lots for the individual attribute in question. It is always calibrated against the in-house primary reference material.

An authenticated plant reference material is material that has been authenticated as the correct plant species and correct plant part(s) by a qualified plant taxonomist. It is permissible to use authenticated plant reference material to accurately identify in-house working reference material, which then becomes a working reference.

Training, Education: Training, education means attainment of knowledge, skills, and abilities pertinent to the position held. It is permissible to gain knowledge, skills, and abilities through relevant academic studies, trade association seminars and workshops, and on-the-job activities in addition to continuing education through relevant courses, seminars, or workshops.

Validation: Validation means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.

Wildcrafted: Wildcrafted means a plant occurring or growing in a natural state; not cultivated or farmed.

IV. General outline of principles for consideration in determining appropriate ingredient identity testing.

Note: The focus here is identity testing. However, these principles are applicable also to testing for adulterants. (See also Appendix A:

Considerations in Determining Adulteration of Dietary Supplements.)

A. Characterize ingredient by type and form: The Dietary Supplement Health and Education Act defines dietary supplement ingredients (see section 201 of the act) as a/an:

1. Vitamin: Identity testing of natural and synthetic vitamins is usually conducted using methods of the AOAC, United States Pharmacopeia (USP), or other publications of established and validated analytical methods (See Appendix B, Reference Citations for Testing Methods);

2. Mineral: Identity testing is usually conducted using methods of the AOAC, USP, or other publications of established and validated analytical methods (See Appendix B, Reference Citations for Testing Methods). Note: Confirming that the mineral is of food, not industrial quality is a purity consideration. Identity considerations for minerals include:

   a. Confirming that the mineral is a proper chelation, if it is chelated and

   b. Confirming the hydration state of the compound.

3. Herb or other botanical: Identity tests for botanical ingredients should be specific enough to distinguish the correct plant species and plant part(s) from known and potential adulterants. Identity testing is usually based on the form of the ingredient at the time of testing, i.e., whether the herb is in whole, cut, powdered, or extracted form.

   Morphological characters and organoleptic characteristics are used in some cases to validate the identity of botanical ingredients at the time of collection or for unprocessed botanicals. When sufficient morphological characters are present to separate the plant species from other plant species, then an accurate identification can be made since morphological characters are the sole basis of distinguishing most of the world's plant species. However, unprocessed botanicals that do not contain all the plant parts necessary to include adequate morphological characters to assure the correct species should have other identity aids or tests to assure the identity of the botanical. For example, it is possible to use only a picture as an identity standard for whole fresh Ginkgo leaf from a cultivated field as it is not easily confused with the leaf shape, venation, and color of other leaves that could be present in the field. But powdered Ginkgo leaf is a different form of the ingredient and requires microscopic and/or chemical

analysis. Ginkgo extracts have no morphological or anatomical features and it is possible that extracts may include a number of chemical compounds at different ratios and concentrations that would require a different chemical test to assure the identity of the ingredient.

The origin or source of a botanical is important since the kind of identity tests that will be necessary to assure the identity of the plant is dependent on the number of plants that could be confused with the desired plant. As an example, a cultivated field of St. John's Wort (*Hypericum perforatum L.*) that was grown from seed or plant stock that had been certified or the field inspected by a botanist competent in determining the species in the field would be all that is required to assure the identity of the unprocessed plant material. However, if the source of St. John's Wort (*H. perforatum L.*) was collected from the wild where other species of *Hypericum* could be confused with it, then collection guidelines and identity tests would need to be established to assure that only the correct species of St. John's Wort (*H. perforatum L.*) was present. (See Appendix B, Reference Citations for Testing Methods).

Herb or botanical ingredients include:

a. Whole, uncut wildcrafted or cultivated plant; plant represented in a whole condition with several plant parts such that definable morphological characteristics are observable. Identity tests for botanicals in this form can be accomplished by macroscopic, organoleptic, microscopic and chemical methods that assure accurate identification. Floras, field guides and plant identification and taxonomic treatments and comparisons to voucher specimens are the most useful references for macroscopic or organoleptic identification of this form of botanicals. It is essential to perform additional tests (i.e., microscopic or chemical analysis) for identification of material in this form.

b. Identifiable whole plant part (i.e., leaves, roots, flowers, bark, seeds, and fruits). Identity testing for botanicals in this form can be accomplished by macroscopic, organoleptic, microscopic, and chemical method that assures accurate identification. Technical guides to commercial botanical products and pharmacopoeias and comparison to authenticated or in-house working botanical reference materials are the most useful identity aids for macroscopic or organoleptic identification of this form of botanical ingredient. It is essential to perform additional tests (i.e.,

microscopic or chemical analysis) for identification of material in this form.

c. Cut or powdered form such that definable morphological characters are few or no longer observable. Identity testing for botanicals in this form can be accomplished by microscopic and chemical methods that assures accurate identification. Technical guides to commercial botanical products and pharmacopoeias or the comparison to authenticated or in-house botanical reference materials are the most useful identity aids for microscopic identification of this form of the botanical ingredient. It is essential to perform additional tests (i.e., microscopic or chemical analysis) for identification of material in this form.

d. Extract. A validated chemical assay such as AOAC, pharmacopoeias, and other publications of established and validated analytical methods are the only analytical methods relevant to identification of this form of the botanical ingredient.

e. The multiple testing in a and b of this section for botanicals in whole form should be waived for any lot of botanical ingredients in whole form in a quantity of less than five hundred pounds, so long as such lot is used solely in direct manufacturing by the processor under the processor's own brand name. In such cases, botanicals in whole form should be positively identified using not less than one of the following tests: (1) morphological or organoleptic test; (2) microscopic test, or (3) chromatographic or spectroscopic tests such as TLC, HPLC, GC, IR, or UV-Vis.

4. Amino acid: Identity testing is usually conducted using methods of the AOAC, USP, or other publications of established and validated analytical methods (See Appendix B, Reference Citations for Testing Methods). Identity testing includes

   a. Confirmation of the optical isomeric form (i.e., L-, D- or racemic).

5. Dietary substance for use by man to supplement the diet by increasing the total dietary intake:

   a. The specific technical approach employed will vary depending on the product category, e.g., blood products, tissue products, cartilage, and etc.

b. Identification testing should establish the identity of the active ingredient in the product and should be able to discriminate between compounds of closely related structure that are likely to be present.

c. Identity tests should be specific for the active product substance, e.g. infrared spectroscopy, polymerase chain reaction amplification of DNA. Identification solely by chromatographic retention time, for example, is not regarded as being specific; however, a combination of tests in a single procedure or test panel may be acceptable. For example, a test panel designed to determine the presence of animal or plant matter and its family/species could be used with further tests to differentiate tissue.

d. All tests employed must be validated.

e. New analytical technology and modifications to existing technology are continually being developed. Such technology should be utilized when analytically validated and when appropriate to the application. (See Appendix B, Reference Citations for Testing Methods).

6. Concentrate, metabolite, constituent, extract, or combination of above ingredients: The specific technical approach employed will vary from product to product. New technology and modifications to existing technology are continually being developed. Such technology should be utilized when validated and when appropriate to the application. For the purpose of identity testing, an appropriate subset of these technologies and methods should be selected and justified.

7. Dietary ingredients that are subject to mis-identification with or adulteration with one or more potentially toxic substances should be tested, as an integral part of identity testing, to assure the absence of such substances. Such testing should use identification methods appropriate for the type and form of the ingredient. A partial list of some dietary ingredients known to be subject to such concern is included as Appendix A.

B. Characterize the testing techniques available: Identity test(s) should be specific for the substance and should be based on the unique aspects of its specific properties. A sufficient number of tests should be performed on representative samples as necessary to establish ingredient identity. (See also Appendix B, Reference Citations for Testing Methods, Appendix C, Reference Citations for Validating Test

Methods; and Appendix D, Reference Citations for Sampling Methods.) Although the focus here is on tests that establish identity, the unique properties of the material are also considered in selecting tests for adulteration (See also Appendix A, Considerations in Determining Adulteration of Dietary Supplements).

Testing techniques include:

1. Macroscopic/Organoleptic: The unaided senses of sight, smell or taste. Included here, however, would be use of a hand lens with 4-20x magnification for visual identification. These methods are typically used for an herb or botanical ingredient in whole or uncut form.

    a. Analysis is based on attributes such as:

        (1) Defined morphological and/or anatomical characteristics of the whole plant or individual plant parts (e.g., leaf, flower, fruit, seed, root and rhizome, bark) and

        (2) Characteristic color, fracture, smell, or taste.

    b. Identification is achieved by positive comparison of morphological characters with authenticated or in-house plant reference material or an authoritative technical reference description or test that can assure the identity of the botanical ingredient.

    c. Herbs and plant parts that have been cut or ground to the point where morphological characteristics are no longer observable to the unaided eye they are best analyzed by microscopic and/or chemical means.

    d. Observations:

        (1) It is possible that processing variables may promote some difference in taste or colors of herbal raw materials, thus confounding proper and positive identification by macroscopic or organoleptic techniques. In order to overcome this concern, controls or limits for such variables need to be included in the manufacturer's protocols.

        (2) It is possible that reliance on taxonomic or botanical characters including macroscopic, anatomical, and organoleptic characteristics alone may not confirm

identity and may not detect adulterants unless the tests are sufficiently precise to distinguish the species from those that it can be confused with in the area that the botanical was collected.

(3) The harvest of plants for use as dietary ingredients often does not coincide with the plant's flowering season. All of the distinguishing morphological characteristics of the plant are not present at such times. While this is not always a significant obstacle to identification, a manufacturer should use good judgment in determining whether this technique can effectively identify plant material at such times without an identity test that has been proven to distinguish the desired species from know and potential adulterants where the botanical is collected.

(4) In the case of plants harvested from wild populations, it is possible that material from different locations and different collectors may be mixed prior to identification by the representative specimen. The integrity of such methodology is suspect in such situations unless the training of collectors and shipping of the material is sufficient to assure the proper identity of all the material and that sampling protocols are designed to detect the adulteration of heterogeneous lots of material.

2. Microscopic analysis: Use of higher magnification (than provided by a hand lens) and special light or staining techniques to examine powdered or chopped representative sample material. Analysis is based on observation of specific microscopic characteristics that have been established for the specific dietary supplement ingredient. This analysis also is used to identify some adulterants.

    a. Identification is based on microscopic observation of cell and tissue structures of plants and animals such as:

        (1) Defined histological characteristics of plant parts (e.g. stems, roots and rhizomes, bark, leaves, flowers, seeds, wood);

        (2) Defined histological characteristics of animal tissues and cells; and

        (3) Defined staining or microscopic chemical reactions.

b. Identification is achieved by use of a validated method, comparison of a representative sample from the commercial batch with authenticated or in-house working plant reference material, or authoritative technical descriptions of established microscopic characteristic(s).

c. Observation:

(1) While microscopy can be used in the identification of ingredients, additional quality or purity data (e.g., contamination by mold, insect, rodent hair, microbe, heavy metal, and economic substitution) can also be obtained from microscopy and

(2) It is possible that finely powdered material may obliterate microscopic characteristics. In this case, other tests such as chemical assays should be employed.

3. Chemical analysis:

a. Chromatography: Techniques that are based on the differential affinities of substances for a gas or liquid mobile medium and a stationary adsorbing medium. Analysis is based on observational comparison of a test pattern and a reference chromatogram for the dietary supplement ingredient of interest.

(1) Chromatography is used for quantitative and qualitative analysis of:

(a) Raw bulk material or finished product;

(b) Process impurities;

(c) Residual solvents;

(d) Preservatives;

(e) Degradation products; and

(f) Adulterants.

(2) Chromatographic analytical techniques include:

(a) High Performance Liquid Chromatography (HPLC);

(b) Gas Chromatography (GC); and

(c) Thin-Layer Chromatography (TLC).

b. Other chemical techniques include:

(1) Spectrographic:

(a) Ultra violet (UV);

(b) Infra red (IR);

(c) Fourier transformed infra red (FTIR); and

(d) Mass separation.

(2) Gravimetric;

(3) Titration;

(4) Capillary electrophoresis (CE); and

(5) Polymerase chain reaction (PCR) amplification of DNA.

c. Observations:

(1) Validated chemical methods are lacking for many dietary supplement ingredients;

(2) All chemical methods rely on the quality, stability and purity of the reference standard and the stability of the analyte in a sample; and

(3) Sources of reference standards are lacking for many dietary supplement ingredients.

C. Characterize ingredient identification environment: Ingredient identification (and quality assurance) performance standards require:

1. Qualified personnel: Personnel must be appropriately qualified to perform ingredient identification procedures including evaluation of supplier certifications, collection of wildcrafted herbs or botanicals, preparation of representative batch or lot samples, organoleptic determinations, microscopic examinations, and chemical analyses. Qualified personnel have:

a. Documented demonstration of knowledge, skills, and abilities pertinent to the position held;

b. Knowledge gained through relevant academic studies, trade association seminars or workshops in addition to continuing education through relevant courses, seminars, workshops, or on-the-job training; and

c. Skills and abilities gained through academic course work, trade association seminars or workshops, and on-the-job activities.

2. Equipment and supplies: Reliable laboratory equipment, appropriate reagents, representative samples, standard reference materials, and authenticated and in-house working plant reference materials are necessary to perform required assays.

a. Laboratory equipment and other apparatus (e.g., microscopes, chromatographic instruments, sieves, slides, cover glasses, needles, and forceps) must be suitable to perform all required tests;

b. Laboratory equipment is calibrated at appropriate intervals and calibrations are documented;

c. Reagents and reference standards are of a quality and purity appropriate for the required tests; and

d. Authenticated and in-house working plant reference materials are of a quality appropriate for the required tests.

3. Laboratory quality: Laboratory certification is documented by appropriate accrediting organization if available or by monitoring in-house quality assurance performance standards.

D. Characterize the initial method validation and the day-to-day use of the validated method as appropriate:

1. Using a validated chemical test:

a. Documents pertaining to validating chemical test methodologies: (See Appendix B: Reference Citations for Testing Methods and Appendix C Reference Citations for Validating Test Methods);

b. Factors to be considered in validation (i.e., accuracy,

precision, and specificity) of a newly-developed or existing chemical test method for its intended purpose include:

(1) Use of the test on multiple occasions or in multiple test facilities to evaluate the test method and present data for validation (in preferential order):

(a) In an inter-laboratory collaborative study (using numerous laboratories);

(b) in a second or third laboratory; or

(c) within an on-site laboratory.

(2) Use of method validation performance parameters such as:

(a) Accuracy;

(b) Detection limit;

(c) Quantitation limit;

(d) Linearity;

(e) Precision (injection and analysis repeatability, intermediate precision, and reproducibility);

(f) Range;

(g) Recovery;

(h) Robustness;

(i) Sample solution stability;

(j) Specificity/selectivity; and

(k) System suitability specifications and tests:

i. Capacity factor;

ii. Precision/injection repeatability;

iii. Relative retention;

iv. Resolution;

v. Tailing factor; and

vi. Theoretical plate number.

3. The reliability (the reproducibility and accuracy of findings) of test methodologies is achieved by:

   a. Use of written procedures;

   b. Use of qualified laboratory technicians and performance standards;

   c. Use of accurate and precise instruments (system suitability parameters);

   d. Use of appropriate reagents, reference materials and reference data; use of standard reference materials, when available or appropriate (see Section IV.D.1.d.);

   e. Use of in-house or outside laboratory(ies) to replicate the test or determination; and

   f. Periodic internal or external audits and reviews of testing documents.

4. Use of nationally- or internationally-recognized reference materials and data: These include

   a. Properly prepared and preserved whole plant specimens;

   b. Pictures of a whole plant or plant part;

   c. Photomicrographs or graphic illustrations;

   d. Chromatographic depictions of comparison peaks; and

   e. Matrices similar to test samples and containing a known amount of analyte, ideally close to the expected amount in test sample ("standard reference materials" (SRMs)).

5. Use of representative test sample(s) in conducting tests: (See Appendix B, Reference Citations for Testing Methods and Appendix D, Reference Citations for Sampling Methods). A representative test sample is:

   a. A homogenous test mass taken from a heterogeneous mass

(i.e., receiving lot/batch) that is used for identity testing. The sample(s) should be homogenous enough to ensure a negligible difference between analyte of separate test portions.

b. Inclusive of collection lots of whole plants, plant parts, or processed material as appropriate to the product manufactured. Large materials must be cut into smaller pieces, mixed thoroughly, and then resampled to achieve a smaller (in volume), yet representative sample.

6. Analytical use of the validated method (systems suitability, that the day-to-day in-house use of the validated method is appropriate) considers the following factors:

   a. Appropriate test(s) were performed on the material;

   b. Appropriate reference materials (e.g., SRMs) were used;

   c. Day-to-day test recoveries for the reference material are consistent and one of the indicators that the chemical analytical method is working;

   d. Any changes or modifications to the method;

   e. System suitability parameters for chemical analyses include:

      (1) Capacity factor;

      (2) Precision/injection repeatability;

      (3) Relative retention;

      (4) Resolution;

      (5) Tailing factor; and

      (6) Theoretical plate number.

7. Use of a CofA: A CofA is a written statement from a supplier about the identity, any additive processing information, composition and strength, quality, and purity of a dietary supplement raw material, ingredient, or finished product. While the CofA focus here is on criteria for confirming identity, results of tests for contamination (e.g., microbial, heavy metal, PCBs, etc.) are needed to evaluate chemical and microbial contamination (see also Appendix E, Desirable Elements of a Certification of Analysis).

It is possible that a CofA may not assure the purity, composition, and quality of the dietary supplement ingredient (see also Appendix G: Case Study).

a. It is possible that a representative sample or other retained reference material that is representative of a receiving lot or batch may accompany a CofA.

b. CofA acceptance criteria are established and justified by the dietary supplement firm purchasing the material.

c. Elements of a "generic" CofA documenting ingredient identity (For a more complete list of CofA elements, see Appendix E, Desirable Elements of a Certificate of Analysis) at a minimum include:

(1) Name and address of the supplier and date CofA attested to;

(2) Name and address of the processor (if appropriate) and type of manufacturing process (e.g., pulverization, decoction, expression, aqueous extraction, ethanolic extraction, and etc.,);

(3) Name of ingredient;

(4) Name, qualifications, and title of person certifying the analysis;

(5) Lot number;

(6) Chemical class of the constituent(s) or characteristic marker(s), if known and if relevant to the identity of the ingredient;

(7) Description of test(s) conducted to confirm identity of the raw material or ingredient. (Note: Tests for adulteration should also be included.);

(8) Test specifications and results;

(9) Identification of standard reference material (identified by number to facilitate trace back) and reference data used to confirm identity; and

(10) Concluding statement that confirms identity based on test results.

d. CofA elements for documenting identity of an herb or botanical include generic identity items plus:

(1) Common and/or usual names of the material and the Latin name of the species (see Herbs of Commerce, 1992 or subsequent edition if the material is not listed in Herbs of Commerce, The CofA must use the complete Latin name.);

(2) Range of dates and locations of harvest, stage of plant development, and plant parts collected;

(3) Whether wild-crafted or cultivated; and

(4) Morphological description for the whole plant and anatomical characteristics of the plant part(s) of commerce.

e. CofA elements for documenting vitamin or mineral ingredient identity include generic identity items plus:

(1) Material specification;

(2) Physical properties;

(3) Assay method; and

(4) Assay test results.

f. CofA elements for documenting identity of other dietary supplement ingredients (i.e., a substance used to supplement the diet, a concentrate, or metabolite) include generic identity items plus:

(1) Item (e.g., specified as species, tissue, extract, and concentrate);

(2) Origin (e.g., country, region);

(3) Description;

(4) Product specifications;

(5) Composition;

(6) Product treatment; and

(7) Assay test results (e.g., protein, mucopolysaccharides, enzymes, and extracts).

g. Evaluation of the reliability of the supplier's CofA for identity (For product purity and wholesomeness see also Appendix H, Supplier Quality Survey of Desirable Characteristics for Production Issues Related to Purity and Wholesomeness of Products) includes:

(1) Assessment of completeness of supplier's CofA (see also Appendix E, Desirable Elements of a Certification of Analysis) and

(2) Assessment of reliability of supplier's CofA (see also Appendix F, Reliability Audit of Suppliers Certificate of Analysis).

V. Records and record retention: Development and maintenance of records are necessary to ensure that dietary supplements are produced under conditions that will result in a product that is not adulterated and is properly labeled. Records are necessary to document that the GMPs are followed and for forward and backward tracing of the manufacturing operations when necessary for public health evaluations of dietary supplement products. Necessary records include:

A. Written procedures and records for personnel: Records shall document that employees engaged in the manufacture process have the proper education, training, and experience needed to perform the assigned function. Appropriate documents retained include:

1. Records that employees have been trained in accordance with written employee orientation procedures;

2. Employee qualifications and training for position held (e.g., training, experience, academic education and credentials);

3. Documentation of on-site training; and

4. Records should be retained for 1 year after the expiration of the shelf life of the dietary supplement product or 3 years from the date of manufacture, whichever is greater.

a. Employee records are generally retained for the duration of an employee's service;

b. Written procedures are generally retained until superseded;

c. Employee records and written procedures, relevant to the manufacturing of a lot of a dietary supplement product, are retained beyond an employee's service or the last date a written procedure was effective by whichever is greater:

(1) One year after expiration of the lot's shelf life, or

(2) Three years from the date of manufacture.

B. Written procedures and records for receiving dietary supplement ingredients include:

1. Written acceptance criteria for dietary supplement ingredients (raw materials or additionally processed) developed by a competent individual;

2. CofA specifications developed to provide information that (see Appendix E, Desirable Elements of a Certificate of Analysis):

a. Identifies the supplier;

b. Characterizes the material as to its source, conditions of production and harvest (if botanical), and any additional processing;

c. Characterizes the material as to its identity, purity, wholesomeness, and activity; and

d. Identifies the validated test methodologies used to confirm identity, purity, and activity.

3. Representative samples from each batch, standard reference materials, and authenticated and in-house working plant reference materials used to confirm ingredient identity are held in an environmentally appropriate repository for each receiving and production lot/batch:

a. For back tracing ingredient identity and

b. To allow cross-referencing with production records and follow-through of the manufacturing process.

4. Records linking the CofA to the identity of the unprocessed raw material (including collection dates and the collection location that includes the country and region with the country of origin for plants and animals) and to the finished product;

5. Audit records concerning the reliability of supplier CofA (See Appendix F, Reliability Audit of Suppliers Certificate of Analysis and Appendix H, Supplier Quality Survey of Desirable Characteristics for Production Issues Related to the Purity and Wholesomeness of Products);

6. Records for animal derived materials or products including:

    a. Traceable records identifying all of the countries where the animals used to produce the material lived and

    b. Traceable records for where animal-derived products were manufactured.

7. Records for fish and fishery products derived materials or products (e.g., fish oils, fish cartilage) that demonstrate those FDA fish and fishery products HACCP regulations are followed (see also 21CFR Part 123:

    a. Records demonstrating compliance with mandatory fish and fishery product HACCP regulations.

8. Written procedures and records for raw material storage to assure segregation of raw, in-process, and finished product; and protection against adulteration; and

9. Records should be retained for 1 year after the expiration of the shelf life of a lot of the dietary supplement product or 3 years from the date of manufacture, whichever is greater.

C. Written procedures and records for testing methods include:

1. Written procedures developed and followed for:

    a. Sample selection;

    b. Method description;

    c. Validation of methodology and results;

    d. Acceptance/rejection criteria; and

    e. Use of test results.

2. Written procedures developed and followed for determining ingredient identity and for detecting adulteration;

3. Written procedures developed and followed for tests to assess the stability characteristics of products in determining appropriate storage conditions and expiration dating;

4. Test records include:

    a. Descriptive characteristics, diagnostic characteristics micrographs, reference literature, graphs, charts, calculations, conversion factors, equivalency factors;

    b. Statements of how results compare with established specifications;

    c. Identification of person (name and title) who performs the test;

    d. Cross-referencing the test result to lot/batch, finished product;

    e. Acceptance/rejection criteria; and

    f. Distribution records for ingredient identification follow-through of manufacturing and distribution process.

5. Records are retained for 1 year after the expiration of the shelf life of a lot of the dietary supplement product or 3 years from the date of manufacture, whichever is greater.

D. Written procedures and records for production include:

1. Master and batch production specifications are developed and used in the manufacturing process including weight or measure of each raw material used and specifications of the finished product; any deviation from lot acceptance criteria; written, approved specifications; standards; extraction procedures; assay procedures; or other laboratory control mechanisms;

2. Equipment use and cleaning and sanitation records, including dates of use, product and lot number of each batch processed;

3. Written procedures and records that demonstrate that automatic equipment is installed, maintained, checked and re-calibrated as necessary to ensure that they are capable of and are performing the intended functions;

4. Written procedures and records for reprocessing of a product

include receipt, storage and handling, sampling, and examination of original packaging material;

5. Written procedures and records to assure that correct labels and labeling and safe packaging materials are used;

6. Written procedures and records to permit tracking the history of the manufacturing process;

7. Reserve samples of each batch of dietary supplement product that are retained and stored under conditions consistent with the product labeling; and

8. Records are retained for 1 year after the expiration of the shelf life of a lot of the dietary supplement product or 3 years from the date of manufacture, whichever is greater.

E. Written procedures and records for distribution are developed and used include:

1. Procedures and records for tracing distribution of product;

2. Procedures and records for recalling a product

3. Procedures and records for salvaging product including examination and reprocessing as appropriate; and

4. Records should be retained for 1 year after the expiration of the shelf life of a lot of the dietary supplement product or 3 years from the date of manufacture, whichever is greater.

F. Written procedures and record for handling complaints include:

1. Procedures developed and used for handling all written and oral complaints regarding a product, including provisions for appropriate review and evaluation by the person or unit responsible for quality control;

2. Records concerning the handling of complaints including any investigation, investigation findings, and follow-up action taken; and

3. Records are retained for 1 year after the expiration of the shelf life of a lot of the dietary supplement product or 3 years from the date of manufacture, whichever is greater.

G. Observations: Review of records is needed to ensure that

1. Procedures established to ensure good manufacturing practices are applied in day-to-day operations and

2. Product not meeting manufacturing specifications for purity, quality, strength, and composition is not distributed.

VI. Appendices:

A. Considerations in Determining Adulteration of Dietary Supplements

B. Reference Citations for Testing Methods.

C. Reference Citations for Validating Test Methods.

D. Reference Citations for Sampling Methods.

E. Desirable Elements of a Certification of Analysis

F. Reliability Audit of Suppliers Certificate of Analysis.

G. Case Study (Plantain and digitalis).

H. Supplier Quality Survey of Desirable Characteristics for Issues Related to the Purity and Wholesomeness of Products.

APPENDIX A:

Considerations in Determining Adulteration of Dietary Supplements:

Adulteration is defined fined in the Food, Drug, and Cosmetic Act, Section 402.

Ingredients may be adulterated by and not limited to

a. Accidental inclusion of substance,

b. Substitution of less expensive but similarly testing ingredients,

c. Deliberate addition of non-declared substances,

d. Filth, pesticides

e. Naturally occurring toxicants

f. Microorganisms

Examples of natural hazardous adulterants associated with an ingredient include but are not limited to (see also 21 CFR Part 189, Substance Prohibited from Use

in Human Food)

a. Siberian Ginseng Root (Eleutherococcus senticosus) adulterated with Periploca sepium root;

b. Plantain leaf (Plantago lanceolata) adulterated with Digitalis lanata leaf;

c. Skullcap herb (Scutellaria lateriflora) adulterated with Germander herb (Teucrium chamaedrys); and

d. Stephania root (Stephania tetranda) adulterated with Aristolochia fangchi root.

e. Pyrrolizidine alkaloids in, for example,

(1) Alkanna tinctoria,

(2) Anchusa officinalis,

(3) Borago officinalis,

(4) Crotalaria spp.,

(5) Cynoglossum spp.,

(6) Erechtites hieraciifolia,

(7) Eupatorium cannabinum,

(8) Eupatorium purpureum,

(9) Heliotropium spp.,

(10) Lithospermum officinale,

(11) Packera candidissima,

(12) Petasites spp.,

(13) Pulmonaria spp.,

(14) Senecio jacobaea,

(15) Senecio vulgaris

(16) Symphytum asperum,

(17) Symphytum spp.,

(18) Symphytum x uplandicum,

(19) Symphytum officinale, and

(20) Tussilago farfara.

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Reference Citations for Testing Methods

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APPENDIX C

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APPENDIX E:

Desirable Elements of a Certification of Analysis

a. Name and address of supplier.

b. Name, qualifications, and title of person certifying the analysis.

c. Harvest location and time (for botanical and animal materials).

d. Collection, washing, drying, preservation procedures, and etc. (if botanical).

e. Handling, transportation, and storage.

f. Name of material and specifications (if applicable).

g. Complete Latin name and common name or as referenced in Herbs of Commerce (if botanical).

h. Standardized reference material for analytical assays and identity test(s) conducted and technical reference materials used including written, visual and/or authenticated plant reference material for verification of material's identity (if

botanical).

i. Retained representative sample material identified by number to facilitate trace back.

j. Appearance.

k. Physical and chemical properties (morphological and anatomical description for whole plant and plant part, if botanical).

l. Active constituent (if known).

m. Activity or strength by weight.

n. Validated test method(s) used.

o. Assay for active constituent or characteristics.

p. Assay for biological activity or biological assay, if available.

q. Assay for water (loss of drying).

r. Assay for analysis of foreign substances (e.g. unreacted materials, by products, adsorbed carbon dioxide).

s. Assay for optical light rotation of the isomers, if appropriate.

t. Chemical marker & measure (if applicable).

u. Name of manufacturer.

v. Manufacture process (e.g., pulverization, decoction, expression, aqueous extraction, and etc.).

w. Disclosure of solvents (if extract).

x. Heavy metals.

y. Microbial contamination and/or preformed endotoxins.

z. Radioactive materials.

aa. Pesticides/herbicides (if applicable).

bb. Foreign materials (e.g. filth, fungi).

cc. Concluding statements that confirm identity, purity, and activity (when appropriate) based on test results.

APPENDIX F

Reliability Audit of Suppliers Certificate of Analysis

For Botanical Collections

1. What are the training and/or experience of those collecting and those determining the identity of the plant? Are plant collectors experienced in or trained in identification and collection techniques for the specific botanical ingredient? What identification aids or guidelines are used to assure that the desired species is collected and not other plants that can be confused with the desired species?

2. Are records kept of collection dates and locations?

3. Are collected materials properly stored and protected from the environment?

4. Are appropriate hygiene procedures observed by plant collectors?

5. Are representative specimens collected, prepared, reviewed, approved, and retained for all shipments? Are these representative specimens compared to an established authoritative identity test or authenticated reference plant materials?

For Ingredient Processing

6. Are all material suppliers evaluated and approved in advance of product receipt?

7. Are raw material and in-process material containers clearly identified with contents and batch identification?

8. Are incoming shipments of raw materials visually inspected for contamination prior to and during unloading? Both the transporting vehicle and individual containers should be examined for:

    a. Wetness and mold

    b. Pests or evidence of pests

    c. Foreign materials, e.g., glass, wood splinters, etc.

    d. Any other potential contaminants.

9. Is sampling properly performed by a trained technician?

10. Is sampling conducted in a manner that yields representative, reliable results?

11. Are materials handled, identified and stored in a manner that will prevent damage, contamination, mix-up, and/or loss?

12. Are material storage and handling procedures formally established in writing?

13. Are bagged and boxed materials stored off the floor, in a suitably clean environment?

14. Is rotated stock system employed to assure that oldest approved products are shipped first?

15. Are products stored under appropriately controlled temperature and humidity conditions?

16. Are inspected and tested materials adequately identified as to acceptance or rejection?

17. Are appropriate records kept to permit forward traceability, i.e., information retrieval system to determine which batches are affected by a given raw material lot?

18. Are product distribution records maintained for at least one year beyond material's expiration or, in the absence of an expiration date, for a minimum of 3 years?

19. Are written procedures established for production and process control, including any special notations or precautions needed?

20. Are production areas of suitable size, construction and location for the job to be performed?

21. Are equipment and production areas of suitable size, construction, and location for the equipment and dietary supplement contact surfaces to be sanitized?

22. Are appropriate exhaust and vacuum systems employed in operations to minimize cross-contamination?

Testing

23. What laboratory equipment, reference materials, and tools are used to determine the identity, and are they suitable to perform all required tests?

24. Are product specifications developed, reviewed, approved, and established in d writing by a competent individual?

25. Are product specifications suitably specific to positively identify the material, and detect potential adulterants?

26. Does the identification process differentiate the desired plant species and plant parts or biological material from closely related plant species and biological material? Does the identity test differentiate the desired species from known adulterants and unwanted plant parts (if a botanical)?

27. Are laboratory test methods validated?

28. Are product tests performed properly and at appropriate frequencies to assure day-to-day consistent use of the validated test method(s) and compliance with all product specifications?

29. Are representative samples and taxonomically authenticated plant reference materials (if botanicals) available for confirmation of the identity and exclusion of potential adulterants?

30. Is laboratory equipment calibrated at appropriate intervals?

31. Is a control system in place to insure that products are not released for distribution until all appropriate tests are performed, reviewed, and approved by a responsible individual?

Records

32. Is there a written overview of the quality assurance process to ensure identity and absence of adulterants? Are there records to ensure day-to-day conformance with the quality assurance process?

33. Are there records to document proficiency of personnel skills?

34. Are there taxonomically authenticated samples including desired species, known adulterants, easily confused species (if botanicals) and protocols for conducting identity and contaminant tests?

35. Are there written or visual technical guides and taxonomic references such as floras and field guides and plant reference materials (if botanicals), official compendial monographs, and authenticated reference materials available to conduct the tests? Are these technical guides sufficient to assure the identity of the botanical by distinguishing the botanical from potential and known adulterants?

APPENDIX G:

CASE STUDY (Plantain and digitalis)

APPENDIX H

Supplier Quality:

Survey of Desirable Characteristics for Production Issues Related to the Purity and Wholesomeness of Products

Manufacturer Information:

Company name.

Parent company (if different).

Plant address.

Mailing address (if different).

Telephone number, fax number, e-mail address.

Plant manager.

Quality assurance manager (if no quality assurance manager, indicate who is responsible for quality assurance activities.

Type of operation.

Is this facility inspected by a third party? If yes, name the organization and date of the most recent inspection and include a copy of the completed inspection report with this survey.

Ingredient Survey:

Material Control

1. Are ingredients identified and /or dated upon receipt?
2. Are in-bound ingredients tested before use?
3. Are there documented in-process control checks performed (e.g., moisture, microbes)?
4. Is finished product traceable to ingredient lot and supplier?

5. Is finished product tested for specification nonconforming ingredients and products?

6. Is there a documented system for handling nonconforming ingredients and products?

7. Are there specific written procedures for performing a trace, recall, or withdrawal of nonconforming ingredients and products?

8. Is there a microbiological laboratory on site? Are samples sent to an outside lab for testing? If an outside lab is used, provide the name and address of the service company.

Product Safety

9. Is there a quality control (or HACCP (Hazard Analysis Critical Control Point when required by 21 CFR Part 123) plan in place, identifying all potential product safety hazards and controlling measures?

10. Attach a quality control plan or process flow diagram and HACCP Plan.

11. If HACCP is not established, describe any other product safety systems.

12. A. Dry System

Are there sifters in the system?

Type and size of sifter screen

Frequency of integrity checks.

Are frequency checks documented?

B. Liquid System

Are there strainers and/or filters in the system?

Location of all strainers and/or filters.

Type and mesh size of strainers and/or filters

Frequency of integrity checks.

Are frequency checks documented?

13. Are there magnets in the system?

Type of magnets (ceramic, rare earth, etc.)

Frequency of integrity checks.

Are frequency checks documented?

14. Is there metal detection in process?

    Is there metal detection on finished product?

    Brand of metal detectors?

    Size and composition of test piece?

    Are tests documented?

    Frequency of sensitivity checks.

    Are sensitivity checks documented?

    Describe kick off/reject procedure.

15. Is there a plan to check for sterilization and pasteurization of animal products when appropriate?

16. Is there a program to inspect carriers prior to loading for your customers?

17. Are there records for animal derived materials or products including traceable records identifying all of the countries where the animals used to produce the material lived and traceable records for where animal-derived products were manufactured?

18. Are there records for fish and fishery products derived materials or products (e.g., fish oils, fish cartilage) that demonstrate that FDA fish and fishery products HACCP regulations are followed (see also 21CFR Part 123?

    Sanitation

19. Is there a documented sanitation schedule for tasks other than daily line sanitation (i.e., Master Sanitation Schedule)?

20. Is there a program to track the receipt and consumption rate of sanitation chemicals?

21. Are chemicals stored in a locked cage/room?

    Pest Management

22. Is there an on-going pest management program for insect and rodent control?

23. Is there a state licensed pest control operator at the plant?

24. Do you use an exterminator service or an in-house program?

    If an exterminator service, please name the service company.

25. Are there any pesticides stored on site?

    Other Good Manufacturing Practices

26. Operational Practices:

    Is there a documented policy of no unprotected glass in the facility?

27. Personnel Practices:

    Is there a documented plant personnel GMP policy?

    Briefly describe the plant requirements regarding hairnets, jewelry, uniforms, etc.

28. Is there required training for new employees?

    Other

29. Is the majority of finished product warehoused on-site or at an outside warehouse location? If off-site, please specify location.

    Name, signature, and date of signature of person completing this form.

    Name, signature, and date of signature of the officer of the company surveyed.

    Surveyed company is approved or not approved as supplier.

    Name, signature and date of signature for person evaluating survey.

Draft Minority Report Statements 6/25/99

FDA Fish and Fishery Products HACCP Regulations

The Working Group Members request agency confirmation that the FDA Fish and

Fishery Products HACCP Regulations apply to dietary supplements when the characterizing ingredient is derived from fish and fishery products (e.g., fish oils and fish cartilage). The Report sections specific to written procedures and records for receiving materials (see Preface, page 1 and Outline V B 7, page 24, and Appendix H, Item 18) guides manufactures to seek records that demonstrate compliance with FDA Fish and Fishery Products HACCP Regulations. However, members are uncertain as to the applicability and extent of applicability of these HACCP Regulations to dietary supplements derived from fish or fishery products, in particular, since this information is not generally available to a manufacturer.

Reporting Serious Adverse Events to FDA

Some Members believe that the written procedures and records for handling complaints should guide manufactures to report serious adverse events to the FDA MEDWATCH system to ensure that the agency has information needed to protect public health (see Report Section V, Records and record retention, F, Written records and procedures for handling complains; page 26). Because of existing concerns about the current usefulness of the system this guidance is not included in the Report.

Performing Multiple Tests in Identifying Whole Plants and Whole Plant Parts

Some members are concerned that the principles outlined for performing multiple tests in identifying whole plants or whole plant parts (see Outline IV A, 3, a and b; page 13) and the exception noted (see Outline IV A, 3, e; page 14) might create a "loophole" that gives a means of escaping testing. Creating a loophole is not the intention. Rather, the intent is to emphasize the need for multiple testing and that sufficient identity tests should be performed to ensure that what is on the product label is true and accurate.

Use of Terms: "Validate, Validated, and Validation"

An unresolved issue remains in this document. Some members are concerned that the use of the terms "validate, validated, and validation" is too broad as it applies to the soundness and consistency of ingredient identity tests for a specific intended use. The terms "validated and validation" have specific meanings in the chemistry world that may not apply to all test methods. For example, the Report refers to "validated" methods for microscopy (when few microscopic methods involve validation) or for using "validated" methods for identifying extracts (although few exist). The Working Group hopes to bring resolution of this issue to the Food Advisory Committee at their June 25 meeting. The Working Group members expect to revise use of this term to more accurately identify the testing techniques where alternate terms such as "verify or verification" or "substantiate or substantiation" would be more appropriate.

Reliance on Authenticated Plant Reference Material

There is a concern that the recommended use throughout Sections IV and V and in Appendix E of "authenticated plant reference material" as defined in the Glossary is unnecessarily narrow. This position expresses a belief that the term "authenticated or other accurately identified plant reference material" provides more practical guidance. An alternate approach is to delete the words "by a qualified plant taxonomist" from the definition of an "authenticated plant reference material" or to change these words to "by a person qualified to make such determination." This position believes that such deletion is consistent with the inclusion of experiences other than academic studies in the Glossary definition of "Training, Education," and does not in any way lessen the recommendation that only plant material that has been positively identified be used as a reference.

Inclusion of Plaintain/Digitalis Case Study

A concern exists that the inclusion of a negative case study will be viewed by industry as unnecessarily critical and lead to an undue and inaccurate perception that the problem of mis-identification of dietary ingredients is widespread. This concern would be addressed by recommending that the agency consider excluding the case study from the proposed Guidance Document, as inclusion might create an obstacle to industry acceptance of the purpose of the Guidance Document as stated in *Good Guidance Practices*, FR (62) 39:8967.

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Hypertext updated by ear/dms 1999-NOV-09